7-3-96

DATA EVALUATION REPORT

KRESOXIM-METHYL

STUDY TYPE: REPEATED DOSE DERMAL - RAT (82-2)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Arlington, VA 22202

Prepared by

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Review Section IV, Toxicology Branch I (7509C)
Toxicology Branch I (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Repeated Dose Dermal - Rat
OPPTS 870.3200 [§82-2]

DP BARCODE: D235934 SUBMISSION CODE: S504279
P.C.CODE: 129111 TOX. CHEM, NO: none

TEST MATERIAL (PURITY): Reg. No. 242 009 (Kresoxim-methyl) (94.3%)

SYNONYMS: BAS 490 F

CITATION: Kirsch. (1994) Study on the dermal toxicity of Reg. No. 242 009 (BAS 490 F) in rats: Application to the intact skin over 3 weeks (21 applications). BASF Aktiengesellschaft, Department of Toxicology, D-67056 Ludwigshafen/Rhine, FRG. Project No. 37H0180/91094; Registration Document No. 94/11070, November 23, 1994. MRID 43883603. Unpublished.

SPONSOR: BASF Agricultural Products Group, P.O. Box 13528, Research Triangle Park, NC 27709-3528.

EXECUTIVE SUMMARY: In a 21-day repeated dose dermal toxicity study (MRID 43883603), groups of 5 male and 5 female Wistar rats were treated with Reg. No. 242 009 (94.3%) in a solution of 0.5% Tylose® CB 30.000 [cleaned natrium-carboxymethylcellulose] in distilled water by dermal occlusion at doses of 0 or 1000 mg/kg/day, 6 hours/day for 21 days.

No mortality was observed and there were no significant treatment-related clinical abnormalities. There were no treatment-related effects on bodyweight, food consumption, organ weights, clinical biochemistry, or hematology. There were no treatment-related pathological abnormalities.

The NOEL for Reg. No. 242 009 was 1000 mg/kg/day; a LOEL was not determined.

This study is classified as **acceptable** and satisfies the guideline requirements for a 21-day dermal study (82-2) in rats.

COMPLIANCE: Signed and dated Quality Assurance, Flagging, Data Confidentiality, and Good Laboratory Practice Statements were present.

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I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Reg. No. 242 009

Description: light brown powder
Lot/Batch No.: N36= III Cl
Purity: 94.3 %
Stability of compound: stable for the duration of the study
CAS No.: not provided
Structure: unknown

2. Vehicle and/or positive control

Vehicle: 0.5% Tylose® CB 30.000 [cleaned natrium-carboxy-methylcellulose] in distilled water
Positive control: none

3. Test animals

Species: rat
Strain: Wistar (Chbb = THOM (SPF))
Age and weight at study initiation: males: 8-10 weeks; 244-275 g; females: 8-10 weeks; 220-237 g
Source: Dr. Karl Thomae GmbH, Biberach/Riss, FRG
Housing: individually in stainless steel wire cages
Diet: Ground Kliba maintenance diet rat/mouse/hamster, 343 meal, Klingentalmuhle AG, Kaiseraugst Switzerland, *ad libitum*
Water: tap water, *ad libitum*
Environmental conditions:
Temperature: 20-24°C
Humidity: 30-70%
Air changes: not provided
Photoperiod: 12 hour light/dark cycle
Acclimation period: 9 days

B. STUDY DESIGN

1. In life dates

Start: October 7, 1992; end: October 28, 1992

2. Animal assignment

Rats were randomly distributed within the experimental groups (Table 1) by a computerized method designed to ensure even weight distribution. Groups of 5 rats/sex/dose were utilized.

TABLE 1. Study design

Dose Group	Dose (mg/kg)	Concentration (g/100 mL)	No. of Animals	
			Male	Female
Vehicle control	0	0	5	5
Reg. No. 242 009	1,000	50	5	5

Data taken from p. 6, MRID 43883603.

3. Dose selection rationale

The dose level was selected from data obtained in a several preliminary studies (acute oral, dermal irritation, eye irritation, 3-month feeding). Based on the results of these studies, where essentially no treatment-related toxicity was observed, the limit dose of 1,000 mg/kg was selected as the only treatment dose.

4. Test substance preparation and analysis

The appropriate amount of Reg. No. 242 009 was weighed out and a 0.5% solution of Tylose® CB 30.000 in distilled water was added. The suspension was mixed with an Ultra-Turrax blender and kept homogeneous during applications using a magnetic stirrer. Test substance was prepared daily, immediately before application.

Results -
Homogeneity analysis - Homogeniety of the test suspension was verified, and ranged from 93.3-95.0% of the nominal value.

Stability analysis - Test material stability of the test suspension was confirmed for a 24 hour period. The sample was 94.5% of the original value after 1 day.

Concentration analysis - The mean concentrations of the test suspension were in the range of 93.3-94.6% of the nominal value.

5. Dose application

A area of fur equivalent to 10% of the body surface area was clipped from the dorsal and dorsallateral area of the trunk of each animal 24 hr before the first application of the test sample. Thereafter, the fur was clipped immediately before application when considered necessary and at least once a week. The appropriate amount of test sample suspension was applied using a 1 mL. syrringe and kept in contact with the shaved skin for 6 hours. Each semiocclusive dressing consisted of 4 layers of absorbent gauze covered by an elastic dressing (Fixomull® stretch adhesive fleece, Biersdirf AG). At the end of the 6-hour exposure period, the dressings were removed and the application area was washed with lukewarm water. A total of 21 six-hour, daily applications were made. At the end of the application period, all animals were sacrificed after a 16 hour fasting period.

6. Statistics

Body weights, food consumption, hematology, and clinical chemistry values of test and control animals were compared by a two-sided Mann-Whitney test for the hypothesis of unequal means.

C. METHODS

1. Observations

Animals were examined for mortality and moribundity, gross signs of toxicity and for signs of irritation at the application site twice daily on days of dosing (prior to dosing and at decontamination).

2. Body weight

Animals were weighed weekly throughout the study.

3. Food consumption

Individual food consumption was calculated weekly throughout the study.

4. Ophthalmoscopic examination

No ophthalmoscopic examinations were performed.

5. Blood samples were obtained from the retroorbital venous plexus of fasted, unanesthetized rats. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)	x	Leukocyte differential count
x	Hemoglobin (HGB)	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)	x	Mean corpusc. HGB conc. (MCHC)
x	Erythrocyte count (RBC)	x	Mean corpusc. volume (MCV)
x	Platelet count		Reticulocyte count
	Blood-clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
x	(Prothrombin time)		
	(Kaolin-cephalin time)		
	Erythrocyte morphology		

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium	x	Albumin
x	Chloride	x	Blood creatinine
x	Magnesium	x	Blood urea nitrogen
x	Phosphorus	x	Total Cholesterol
x	Potassium	x	Globulins
x	Sodium	x	Glucose
		x	Total bilirubin
		x	Total serum protein (TP)
	ENZYMES	x	Triglycerides
x	Alkaline phosphatase (ALK)		Serum protein electrophores
	Cholinesterase (ChE)		
	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
	Serum alanine amino-		
x	transferase also SGPT)		
	Serum aspartate amino-		
x	transferase (also SGOT)		
	Gamma glutamyl		
x	transferase (GGT)		
	Glutamate dehydrogenase		

6. Urinalysis

Urinalysis was not required and was not performed.

7. Sacrifice and pathology

All animals survived until the scheduled termination of the study. Rats were sacrificed at the end of the study by decapitation under CO_2 anesthesia. Gross pathological examinations were conducted and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
	Tongue		Aorta		Brain
	Salivary glands		Heart		Periph. nerve
	Esophagus		Bone marrow		Spinal cord (3 levels)
	Stomach		Lymph nodes		Pituitary
	Duodenum		Spleen		Eyes (optic n.)
	Jejunum		Thymus		
	Ileum				GLANDULAR
	Cecum		UROGENITAL	xx	Adrenal gland
	Colon	xx	Kidneys*		Lacrimal gland
	Rectum		Urinary bladder		Mammary gland
xx	Liver*	xx	Testes		Parathyroids
	Gall bladder		Epididymides		Thyroids
	Pancreas		Prostate		
			Seminal vesicle		OTHER
	RESPIRATORY		Ovaries		Bone
	Trachea		Uterus		Skeletal muscle
	Lung			x	Skin (treated and untreated)
	Nose				
	Pharynx			x	All gross lesions and masses
	Larynx				

*Required for subchronic studies based on Subdivision F Guidelines

II. **RESULTS**

A. OBSERVATIONS

No treatment-related mortality or clinical signs of toxicity were seen in any rats. The adhesive fleece wrapping caused mechanical skin lesions in both treated and control animals.

B. BODYWEIGHT AND WEIGHT GAIN

No significant difference in group body weight means occurred for the treated group as compared to controls.

C. FOOD CONSUMPTION

1. Food consumption

No differences in food consumption were observed between treated animals and controls.

2. Food efficiency

Feed efficiency ({body weight gain [kg]/food consumption [kg per unit time]} x 100) values were not calculated by the study authors. Because there were no toxicologically relevant changes in food intake or body weight, food efficiency was not considered to provide any additional information.

D. OPTHALMOSCOPIC EXAMINATION

No opthalmoscopic examinations were performed.

E. BLOODWORK

No hematological or clinical chemistry effects were observed.

F. URINALYSIS

Urinalysis was not required and was not performed.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

There were no compound-related effects on organ weight.

2. Gross pathology

No toxicologically significant effects were observed. A 1 mm. red focus was observed on the left adrenal of one treated female.

3. Microscopic pathology

a) Non-neoplastic - A small, single focus of crust formation in the cornifying layer of the treated skin of one male rat was observed. No inflammatory reaction was observed underneath the lesion. Treated males exhibited less peripheral fatty infiltration of hepatocytes than male controls. Focal intratubular and interstitial calcification of the kidneys and interstitial nephritis were observed similarly in treated and control females. None of these lesions are considered treatment-related or of toxicologically significant.

b) Neoplastic - No neoplastic lesions were observed.

III. **DISCUSSION**

A. Male and female Wistar rats were treated dermally with 0 or 1000 mg/kg/day of Reg. No. 242 009 6 hours/day for 21 days. No differences in group body weight means or cumulative body weight gains occurred for any treated group of either sex as compared to controls. No treatment-related mortality or clinical signs were observed. No significant clinical chemistry or hematological effects were observed. No significant gross or microscopic treatment-related pathology was observed.

Under conditions of this study, the NOEL for Reg. No. 242 009 is 1000 mg/kg/day; a LOEL is not identified.

B. STUDY DEFICIENCIES

Lung histopathology was not examined. This is not thought to significantly compromise this study.